Review

Type 2 diabetes mellitus: epidemiology, pathophysiology, unmet needs and therapeutical perspectives

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Abstract

In France, prevalence of drug-treated diabetes reached 3.60% in 2005, with 92% of type 2 diabetic patients. In 2007, there are probably nearly 3 000 000 diagnosed or undiagnosed diabetic patients. Ageing of the population and increase in obesity are the main causes of this "diabetes epidemic". Type 2 diabetes is a multifactorial disease, defined as resulting from defects in insulin secretion (including abnormalities in pulsatility and kinetics, quantitative and qualitative abnormalities of insulin, β-cell loss progressing with time) associated with insulin resistance (affecting liver, and skeletal muscle) and increased glucagon secretion. The lack of compensation of insulin resistance by augmented insulin secretion results in rise in blood glucose. To achieve satisfactory glycaemic control in order to prevent diabetes related complications, drug therapy is generally required in addition to life style changes. Currently available oral therapies offer a large panel of complementary drugs, but they have several contraindications and side effects. In spite of major advances in the management of type 2 diabetes, and the strictness of new guidelines, some goals remain unachieved and the new family of insulin-secretors (DPP-IV inhibitors, GLP-1 analogues) should enrich therapeutic approaches.

Résumé

Diabète de type 2 : épidémiologie, physiopathologie, problèmes non résolus et perspectives thérapeutiques

En France, la prévalence du diabète traité par médicaments atteignait 3,6 % en 2005, dont 92 % de diabète de type 2, et en 2007 existent probablement près de 3 000 000 de diabétiques connus ou ignorés. Le vieillissement de la population et l'obésité croissante sont les principales causes de ce développement « épidémique » du diabète. Le diabète de type 2 est une maladie multifactorielle, qui associe une dysfonction insulaire (qui comporte des anomalies de la pulsatilité et de la cinétique, des altérations quali- et quantitatives de l'insulinosécrétion, et une perte de la masse des cellules β s'aggravant avec le temps) d'origine génétique, un déficit de l'insulinosensibilité (touchant le foie et le muscle strié) lié à des facteurs d'environnement (sédentarité et excès pondéral) et une hypersécrétion de glucagon. Le défaut de compensation de l'insulinorésistance par un débit insulinosécrétoire insuffisant a pour conséquence l'élévation de la glycémie. L'obtention d'un contrôle glycémique satisfaisant dans le but de prévenir les complications liées au diabète, nécessite en général le recours à des agents pharmacologiques en plus du traitement hygiénodiététique. Les médicaments oraux actuellement disponibles offrent un large spectre sur le plan de leur mécanisme d'action, mais ils ont un certain nombre de contre-indications et d'effets indésirables. Malgré les progrès accomplis dans le traitement du diabète de type 2 et la rigueur des nouvelles recommandations, il reste des objectifs non atteints, et de nouveaux insulinosécréteurs, inhibiteurs du DPP-IV et analogues du GLP-1, pourraient contribuer à compléter avantageusement l'arsenal thérapeutique.

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1. Epidemiology of type 2 diabetes in France

In 2007, type 2 diabetes represents a major public health issue all over the world, becoming a "diabetes epidemic" as stated by Zimmet [1]. A few years ago, the concern of the "diabetes epidemic" was restricted to the US while the other parts of the world were not considered as threatened. Unfortunately, the picture has moved and nowadays no country escapes the diabetes invasion. In the world, diabetes prevalence in adults aged 20 and over was 4.0% in 1995 and it is expected to increase to 5.4% in 2030, slightly higher in the developed than in the developing countries [2]. Expressed in number of patients, the expected evolution of diabetes is more striking and spectacular, as the total number of adult diabetic patients (roughly type 2 diabetic patients) in the world should increase from 135 to 300 million between 1995 and 2030, mainly due to a tremendous increase of 171% in developing countries, from 84 to 228 million, while it should increase only of 41% in developed countries, from 51 to 72 million [2]. At the present time, the rank of countries for the number of diabetic patients is yet, in decreasing order, India, followed by China then the US. The ranking should be similar in 2030. In 2030, more than 75% of all the diabetic patients in the world will live in the developing countries, compared to 62% in 1995. In addition, these projections calculated by the WHO experts are probably underestimated as they are based only on the expected demographic evolution and do not take into account the evolution of obesity in the near decades. Therefore, the reality of diabetes in 2030 should be quite far over these figures.

1.1. Prevalence of type 2 diabetes in France

In France, diabetes prevalence has been well known for drug-treated patients from 1998 on [3], when the database of the National Public Health Insurance System (CNAMTS) containing all the files of patients' claims for drug reimbursement was computerized (SIAM). Thus, thanks to the specificity of the drugs used for diabetes treatment (oral antidiabetic drugs [OAD] and insulin), the prevalence rate of diabetes could be calculated in 1998 then measured every year up to 2005. It increased from 2.78% in 1998 to 2.96% in 2000 [3] then 3.6% in 2005 [4], indicating an average annual increase of 3.2% between 1998 and 2000 then of 5.7% between 2000 and 2005, with around 92% of type 2 diabetic patients. French diabetic patients in 2005 were aged 64.7 ± 14.0 years (m ± SD) and had an annual death rate of 2.3%, with a mean age at death of 75.2 years [4]. When adding the type 2 diabetic patients only treated by lifestyle intervention (diet and physical activity), the prevalence of known diabetes was probably over 3%

in 1998–2000 and could reach 4% in the very near future. In addition, there are undiagnosed diabetic patients whose number cannot be given precisely by definition, probably no more than 500 000 subjects as systematic diabetes screening is widely performed in France [5]. Therefore, overall, there are probably around 2 500 000 known diabetic patients and nearly 3 000 000 diagnosed or undiagnosed diabetic patients in metropolitan France at the present time. Concerning the French Overseas Departments, recent data indicated a prevalence of pharmacologically treated diabetes in 2005 equal to 10.1% in Guadeloupe, 7.9% in Martinique and 7.4% in La Reunion Island, confirming the previous figures, yet quite higher than in metropolitan France. Therefore, the label "diabetes epidemic" can probably be also applied to France.

1.2. Causes of the increase in type 2 diabetes prevalence

Obesity, mainly when fat is distributed predominantly at the abdominal level as shown in the fifties by Jean Vague, is the main risk factor for type 2 diabetes. In France as in all over the world, the diabetes epidemic is due to the increase in prevalence of obesity, linked to "westernized" lifestyle, namely changes in nutritional habits, with increased intake of saturated fats, refined sugars and alcohol, and reduced intake of fibres, and at the same time, reduction in physical activity. The impact of "coca-colonization" has been nicely shown by the comparison between Pima Indians from Arizona and Pima Indians from a remote area in Mexico, and native Mexicans (Fig. 1), showing the major role of environmental factors compared to genetic factors in the occurrence of diabetes [6]. The role of environment has also been demonstrated from many years by urban–rural comparisons of diabetes prevalence, higher in the urban areas inside any ethnic group, in a lot of epidemiological studies all around the world.

The increase in obesity is not only restricted to the US, but is becoming a major Public Health concern in France. In our

	Arizona Pima Indians (n = 888)	Mexican Pima Indians (n = 224)	Mexicans (n = 193)
BMI (kg/m²)	34.6 ± 7.9	25.1 ± 4.2	25.8 ± 4.4
Calorie intake (kCal/day)	1751 ± 788	2485 ± 563	2593 ± 600
Lipid intake (%)	34.5 ± 9.5	26.3 ± 6.3	25.4 ± 5.8
Physical activity (hr/wk)	7 ± 3	27 ± 2	27 ± 1
Prevalence of T2DM (%)	38.1	7.1	2.6

Fig. 1. Influence of genetic and environmental factors on prevalence of type 2 diabetes [6].